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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/656,228	09/08/2003	Yusuke Amino	241406US0CONT	1073

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OBLON, SPIVAK, MCCLELLAND, MAIER & NEUSTADT, P.C.  
1940 DUKE STREET  
ALEXANDRIA, VA 22314

EXAMINER

ZUCKER, PAUL A

ART UNIT	PAPER NUMBER
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1621

DATE MAILED: 11/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 10/656,228	<b>Applicant(s)</b> AMINO ET AL.	
	<b>Examiner</b> Paul A. Zucker	<b>Art Unit</b> 1621	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
  - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
  - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
  - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 03 September 2004.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-15,17-22 and 29-39 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 1,2,4-15,17-21,29,30,33 and 35 is/are allowed.
- 6) ☒ Claim(s) 3,22,31,32,34 and 36-39 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 08 September 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☒ Certified copies of the priority documents have been received in Application No. 10/091,500.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>9/8/2004</u> . | 6) <input type="checkbox"/> Other: _____  |

**DETAILED ACTION**

***Election/Restrictions***

1. Upon further consideration, the Examiner hereby withdraws the previous restriction set forth in the Office Action mailed 5 August 2004. Claims 1-15, 17-22 and 29-39 have been fully examined on the merits and are the subject of the Office Action below.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 3, 22, 31, 32, 34 and 36-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Nofre et al (US 5,480,668 01-1996). Nofre discloses (Column 8, top, Table 1, entry No 18) the compound N-[N-[3-(3-methoxy-4-hydroxyphenyl) propyl]-L- $\alpha$ -aspartyl]-L-phenylalanine 1-methyl ester. Nofre further discloses (Column 7, lines 39-51) a process for its production by reductive amination with 3-(3-methoxy-4-hydroxyphenyl) propionaldehyde of aspartame and subsequent purification. The crude product presumably contains aspartame and 3-(3-methoxy-4-hydroxyphenyl) propionaldehyde. Nofre teaches (*ibid*) concentration of the reaction mixture to dryness, aqueous extraction to form a gummy precipitate, presumably to remove

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aspartame, followed by recrystallization from ethanol/water or acetonitrile. Nofre therefore anticipates claims 3, 22, 31, 32, 34 and 36-39.

***Allowable Subject Matter***

3. Claims 1,2, 4-15, 17-21, 29, 30 33 and 35 are allowed. The following is a statement of reasons for the indication of allowable subject matter:

Instantly claimed is a method for the production of N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- $\alpha$ -aspartyl]-L-phenylalanine 1-methyl ester comprising subjecting 3-(3-methoxy-4-hydroxyphenyl) propionaldehyde and Aspartame to reductive alkylation via hydrogenation in the presence of a catalyst followed by crystallization.

The closest prior art is Nofre et al (US 5,480,668 01-1996) and Claude et al (US 5,510,508 04-1996).

Nofre teaches (Column 8, Table 1, entries 18 and 19) the compounds N-[N-[3-(3-methoxy-4-hydroxyphenyl)propyl]-L- $\alpha$ -aspartyl]-L-phenylalanine 1-methyl ester and its unsaturated counterpart. Nofre further teaches (Column 7, lines 24-51) a general process for its synthesis. Nofre teaches a process for reductive alkylation of aspartame with the appropriate aldehyde (1.099 molar ratio aldehyde/aspartame) in methanol at room temperature for 24 hours. Nofre teaches removal of the reaction solvent (methanol), washing with aqueous HCl (to remove aspartame) and its

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replacement with ethanol/water as a recrystallization solvent (solvent substitution).

Aspartame as well as other impurities, is removed via the disclosed crystallization.

The difference between the process taught by Nofre and the instant process is that Nofre teaches a process for reductive alkylation which employs sodium cyanoborohydride as a reductant while the instant application claims the use of a catalytic hydrogenation reaction.

Claude, however, teaches (Column 3, line 63- column 4, line 26) a reductive alkylation reaction between 3,3-dimethylbutyraldehyde and aspartame in methanol solution in the presence of platinum catalyst and hydrogen gas at 1 bar at room temperature.

Neither Nofre nor Claude, however, disclose or fairly suggest the use of the unsaturated aldehyde to produce the saturated product or the use of hydroxyl-protected aldehyde starting material. One of ordinary skill in the art would not therefore have been motivated to make the modification of the process of Nofre and Claude to produce the instantly claimed process. The instantly claimed process is therefore patentable over the teachings of Nofre and Claude.

### ***Conclusion***

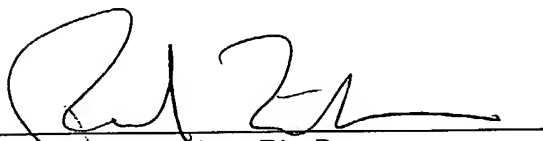
4. Claims 1-15, 17-22 and 29-39 are pending. Claims 3, 22, 31, 32, 34 and 36-39 are rejected. Claims 1, 2, 4-15, 17-21, 29, 30 33 and 35 are allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul A. Zucker whose telephone number is 571-272-0650. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A handwritten signature in black ink, appearing to read 'Paul Zucker', is written over a horizontal line.

Paul A. Zucker, Ph. D.  
Patent Examiner  
Technology Center 1600